Original Article

Clinical outcomes of fluoroquinolones combination therapy in patients with hospital-acquired pneumonia: a retrospective cohort study using national health insurance claims data in Korea

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Background: Fluoroquinolones are one of the commonly used antibiotics for the initial empiric combination treatment. However, there is insufficient evidence to support the use of fluoroquinolones combination therapy for the treatment of hospital-acquired pneumonia (HAP). This study aimed to evaluate the effectiveness of fluoroquinolones as part of the empiric combination therapy for HAP using national health insurance claims data in Korea.

Methods: We compared the clinical outcomes of patients with HAP who received fluoroquinolones combination and those treated with cefepime or piperacillin/tazobactam monotherapy. The primary outcome was hospital mortality, and the secondary outcome was readmission caused by pneumonia as the primary cause of hospitalization within 7 days after discharge from index hospitalization. The association between the combination with fluoroquinolones and outcomes was evaluated with logistic regression analysis.

Results: Among the 9,955 patients with HAP administered with cefepime or piperacillin/tazobactam, 4,918 (49%) received fluoroquinolones combination. During hospitalization, 1,059 (11%) patients with HAP died. Compared with the monotherapy group, the fluoroquinolones combination therapy group was associated with a higher mortality risk [adjusted odds ratio (OR), 1.30; 95% confidence interval (CI): 1.02–1.65]. After adjusting for potential confounding factors, the association remained significant in the non-high-risk HAP group (adjusted OR, 1.30; 95% CI: 1.02–1.66). Meanwhile, the mortality risk was similar between the fluoroquinolones combination therapy group and the monotherapy group of patients with high-risk HAP (adjusted OR, 0.99; 95% CI: 0.35–1.16). Among the patients alive and discharged (n=8,896), 152 (1.7%) were readmitted within 7 days after discharge. The fluoroquinolones combination therapy group was more likely to be readmitted because of pneumonia than the monotherapy group in patients with high-risk HAP (adjusted OR, 1.60; 95% CI: 1.04–2.47).

Conclusions: Fluoroquinolones combined with β-lactams was prescribed in nearly half of patients with low-risk HAP, and it was associated with a higher mortality risk in real-world practice. However, it was not associated with hospital mortality even in patients with high-risk HAP.

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Introduction

Hospital-acquired pneumonia (HAP) is a common nosocomial infection (1), which prolongs hospitalization and contributes to significant morbidity and mortality (2). Current guidelines recommend empiric combination treatment for patients with HAP having risk factors for multidrug-resistant (MDR) pathogen-induced infections and other factors associated with a high mortality risk (3,4); however, the quality of the evidence is low. The American guideline suggests prescribing two antipseudomonal antibiotics from different classes for patients with risk factors for gram-negative infection or a high risk for mortality (3). In the European guideline, initial empiric combination treatment is recommended for high-risk patients who have either septic shock and/or risk factors for potentially resistant microorganisms (4). Despite various side effects, fluoroquinolones are one of the commonly used antibiotics for the initial empiric combination treatment because of its pharmacological characteristics and clinical tolerability similar to those of other antimicrobial classes (5,6). In actual clinical practice, however, many patients with infection, including HAP, were inappropriately treated with combination therapy involving fluoroquinolones (7,8). In addition, evidence supporting the combination therapy of fluoroquinolones added to beta-lactams for treating HAP remains weak. Therefore, using national health insurance claims data, we evaluated the use of fluoroquinolones as part of the empiric combination therapy for HAP and determined whether it can improve the clinical outcomes of patients with HAP. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-787/rc).

Highlight box

Key findings

- This study found that fluoroquinolones combination therapy was not associated with hospital mortality even in high-risk patients with hospital-acquired pneumonia (HAP) who were recommended to receive such combination treatment, but, the risk of readmission caused by pneumonia within 1 week after hospital discharge was high.

What is known and what is new?

- Fluoroquinolones are one of the commonly used antibiotics for the initial empiric combination treatment for HAP.
- The impact of fluoroquinolones combined with β-lactams is unclear.

What is the implication, and what should change now?

- Fluoroquinolones combination therapy should be applied when the benefit outweighs the risk in the management of patients with HAP.

Methods

Data source & study population

The Korean National Health Insurance Service (KNHIS) is a public medical insurance system that covers approximately 97% of Koreans. Data used in this study were obtained from the national health claims database established by the KNHIS, which provides robust data about the diagnoses according to the 10th edition of the International Classification of Diseases (ICD-10) and about interventions, prescriptions, and patient demographics (9,10).

In this population-based retrospective cohort study, we used data from January 1, 2018, to December 31, 2018, in the KNHIS database. The inclusion criteria were age of ≥20 years who were diagnosed with HAP during hospitalization for more than 3 days in a tertiary or general hospital and were treated with cefepime or piperacillin/tazobactam, in a manner previously reported (11). If a patient had multiple inpatient records, we only considered the first episode.

Our primary research objective was to evaluate the effect of fluoroquinolones combined with a recommended β-lactam (cefepime or piperacillin/tazobactam) as the empiric therapy for HAP. Hence, we only used data from patients with incident HAP. In line with a previous study (11), patients diagnosed with HAP and received cefepime or piperacillin/

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tazobactam at least 3 days during hospitalization were eligible for this study. The fluoroquinolones combination therapy group include patients who received levofloxacin or moxifloxacin, which are most commonly prescribed for respiratory infections in Korea. We excluded patients who had pneumonia within 3 months before hospitalization, using codes in the 10th revision of the International Classification of Diseases. In addition, we excluded those who were admitted to the hospital from the emergency room and were suspected of community-acquired pneumonia. We further excluded patients prescribed both cefepime and piperacillin/tazobactam (n=375) and prescribed one of the monobactams, aminoglycosides, carbapenems, or glycopeptides (n=5,417) to rule out contamination of other antibiotics. Finally, 9,955 eligible patients were retrieved.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Samsung Medical Center (No. SMC201912141 HE002). The requirement for informed consent was waived because of the retrospective nature of the study and use of only anonymized data.

Covariates

Details of NHIS claims data on patients with HAP and measurement are described in our previous publication (11). We also included information on sociodemographic characteristics, comorbidities, procedures, medications, and hospital settings based on claim codes (12). Patients receiving antibiotics 3 months before hospitalization or treated in the intensive care unit (ICU) during hospitalization were considered having high-risk HAP in which the international guidelines recommend fluoroquinolones combination.

Outcomes

The primary outcome was hospital mortality, which was verified through the data from the Korean Statistical Information Service by the Statistics Korea. The secondary outcome was readmission caused by pneumonia as the primary cause of hospitalization within 7 days after discharge from index hospitalization.

Statistics

Given that patient survival could be clustered by hospital, in-hospital mortality between patients receiving fluoroquinolones combination and those with β-lactam monotherapy was compared using mixed-effects logistic regression. For the multivariable model, we adjusted for age, sex, hospitalization history, comorbidities, and ICU admission based on literature review. Then, we checked the absence of multi-collinearity and the improvement of the Akaike information criterion of the model compared to the crude model. Among patients alive and discharged, the same analysis was conducted for readmission within 7 days as the secondary outcome. All the analyses included the interaction terms of fluoroquinolones and high-risk HAP. The logistic regression results were reported as odds ratios (ORs) of each variable with their 95% confidence intervals (CIs). All P values were two-sided, and a P value of less than 0.05 was considered significant. Furthermore, all statistical data were analyzed using SAS® Visual Analytics (SAS Institute Inc., North Carolina, USA) and STATA (version 17.0, Stata Corporation, College Station, Texas, USA).

Results

Among the 9,955 patients with HAP administered with cefepime or piperacillin/tazobactam, 4,918 (49%) received fluoroquinolones combination. *Table 1* summarizes the clinical details of patients in the monotherapy and combination therapy groups. Compared with the monotherapy group, the combination therapy group had more males and higher proportions of chronic obstructive pulmonary disease (COPD), mechanical ventilation, and ICU admission. However, other comorbidities were higher in the monotherapy group (*Table 1*).

Furthermore, among the 5,569 (56%) patients with non-high-risk HAP, approximately half were treated with fluoroquinolones combined with cefepime or piperacillin/tazobactam. During hospitalization, 1,059 (11%) patients with HAP died. Compared with the monotherapy group, the fluoroquinolones combination therapy group was associated with a higher mortality risk (OR, 1.30; 95% CI: 1.02–1.65), particularly in those with non-high-risk HAP (*Table 2*). After adjusting for potential confounding factors, we found that the association remained significant in the non-high-risk HAP group (adjusted OR, 1.30; 95% CI: 1.02–1.66). Meanwhile, the mortality risk was similar between the fluoroquinolones combination therapy group and the monotherapy group of patients with high-risk HAP (adjusted OR, 0.99; 95% CI: 0.34–1.16; P for interaction=0.05).

Among the patients alive and discharged (n=8,896),

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Table 1 Characteristics of the study population (N=9,955)

Variables	Without quinolones (n=5,037)	With quinolones (n=4,918)	P value
Age (years)	74.01 (13.64)	73.87 (12.78)	0.60
Sex			<0.01
Male	3,041 (60.37)	3,149 (64.03)	
Female	1,996 (39.63)	1,769 (35.97)	
Comorbidity			
Cancer	1,448 (28.75)	1,448 (29.44)	0.45
Asthma	2,226 (44.19)	2,260 (45.95)	0.08
COPD	1,183 (23.49)	1,315 (26.74)	<0.01
CKD	773 (15.35)	626 (12.73)	<0.01
ESRD	780 (15.49)	633 (12.87)	<0.01
Anemia	1,530 (30.38)	1,382 (28.1)	0.01
Hospitalization history	2,479 (49.22)	2,321 (47.19)	0.04
Antibiotic history 6 months before hospitalization	1,664 (33.0)	1,650 (33.6)	0.59
Hospital location			<0.01
Metropolitan	3,498 (69.45)	3,545 (72.08)	
Rural	1,539 (30.55)	1,373 (27.92)	
Hospital type			<0.01
Tertiary	1,307 (25.95)	1,611 (32.76)	
General	3,730 (74.05)	3,307 (67.24)	
Tube feeding	1,403 (27.85)	1,409 (28.65)	0.38
Suction	1,305 (25.91)	1,352 (27.49)	0.07
Positioning care requirement	1,743 (34.6)	1,665 (33.86)	0.43
Mechanical ventilation	466 (9.25)	590 (12)	<0.01
ICU admission	1,528 (30.34)	1,623 (33)	<0.01
Comedication			<0.01
Cefepime	883 (17.53)	767 (15.6)	
Piperacillin/tazobactam	4,308 (85.53)	43 (88.98)	

Values are presented as n (%) or mean (SD). COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HAP, hospital-acquired pneumonia; ICU, intensive care unit.

152 (1.7%) were readmitted within 7 days after discharge. In non-high-risk HAP group, there was no significant difference between the two groups (adjusted OR 1.13, 95% CI: 0.73–1.77). However, the fluoroquinolones combination therapy group was more likely to be readmitted because of pneumonia than the monotherapy group in patients with high-risk HAP (adjusted OR, 1.60; 95% CI: 1.04–2.47; P for interaction=0.26) (*Table 2*).

Discussion

This NHIS data-based study found that fluoroquinolones combination therapy was provided to nearly half of patients with HAP in which fluoroquinolones combination is not recommended by the international guideline and that it was associated with a higher mortality risk. In addition, this combination therapy was not associated with hospital

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Table 2 Clinical outcome by fluoroquinolone combination therapy according to the high-risk hospital-acquired pneumonia

Outcomes	Non-high-risk HAP group (n=5,569)		High-risk HAP group (n=4,386)		P for interaction
	Without quinolones (n=2,774)	With quinolones (n=2,795)	Without quinolones (n=2,263)	With quinolones (n=2,123)	
Hospital mortality (n=9,955)					
Number of mortality cases (%)	140 (6.2)	162 (7.6)	387 (14.0)	370 (13.2)	
Crude OR (95% CI)	Reference	1.30 (1.02–1.65)	Reference	0.97 (0.83–1.14)	0.04
Adjusted OR (95% CI)	Reference	1.30 (1.02–1.66)	Reference	0.99 (0.34–1.16)	0.05
Readmission after discharge (n=8,896)					
Number of readmission cases (%)	40 (1.9)	42 (2.1)	34 (1.4)	56 (2.3)	
Crude OR (95% CI)	Reference	1.15 (0.74–1.79)	Reference	1.64 (1.07–2.52)	0.27
Adjusted OR (95% CI)	Reference	1.13 (0.73–1.77)	Reference	1.60 (1.04–2.47)	0.26

Adjusted for age, sex, hospitalization history, asthma, cancer, COPD, CKD, ESRD, and ICU admission, and considering mixed effects of hospitals. HAP, hospital-acquired pneumonia; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICU, intensive care unit.

mortality even in high-risk patients with HAP who were recommended to receive such combination treatment, but interestingly, the risk of readmission caused by pneumonia within 1 week after hospital discharge was high.

A meta-analysis study on combination antibiotic therapy in serious bacterial infections suggested that combination therapy is associated with increased mortality risk in patients with low mortality risk, although this study did not address only HAP and fluoroquinolones combination (13). In our study, patients with non–high-risk HAP receiving fluoroquinolones combination therapy were associated with an increased risk of hospital mortality, although the mechanism supporting survival disadvantage in these patients is unknown. Adverse drug reaction seems to be most likely, but the observation that empiric combination therapy is associated with worsened outcomes in patients with non-high-risk HAP is interesting and requires further investigation.

Although combination antibiotic therapy is recommended for high-risk HAP (3,4), the available evidence has many limitations. In the present study, we could not find survival advantage even in patients with high-risk HAP treated with fluoroquinolones combination therapy. This result is consistent with the finding of previously published meta-analyses, which did not show superiority of combination therapy over β-lactam monotherapy in the empiric antibiotic treatment (14,15). In addition, the rate of readmission caused by pneumonia within 1 week after hospital discharge was higher in the fluoroquinolones combination therapy group. This result might be associated with more comorbidities with rehospitalization risk, such as COPD, in patients with high-risk HAP. However, several studies investigating critically ill patients also suggest that the combination of broad-spectrum antibiotics may be associated with greater toxicity, and is a risk factor for later emergence of MDR organisms and increasing rate of superinfection (16,17). Therefore, combination therapy should be applied when the benefit outweighs the risk.

To our knowledge, this comparative study is the first to evaluate the clinical benefits of antipseudomonal β-lactams combined with fluoroquinolones in HAP management, using a nationwide claim database. However, our study has several potential limitations that should be acknowledged. First, HAP defined by claim codes has limitations in accuracy and validity. We tried to use an operational definition of HAP that fits the definition of existing guidelines, but diagnoses based on claim codes can differ from clinical diagnoses. The KNHIS database, however, is regularly audited, and the data is considered reliable and has been used in many peer-reviewed publications (18). Second, our findings could not be adjusted for microbiology and other unmeasured confounders unavailable in the NHIS database. Third, patients who received carbapenems, which are another anti-pseudomonal beta-lactams for

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empiric treatment of clinically suspected HAP, but not commonly prescribed in real practices because antimicrobial stewardship to restrict the use of carbapenems has been suggested (19), were excluded from the analysis.

Conclusions

Fluoroquinolones combined with β-lactams was prescribed in nearly half of patients with low-risk HAP in the real-world setting and was associated with a higher mortality risk.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-787/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-787/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-787/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Samsung Medical Center (No. SMC201912141 HE002). The requirement for informed consent was waived because of the retrospective nature of the study and use of only anonymized data.

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References

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198-208.
2. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013;13:665-71.
3. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61-e111.
4. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017;50:1700582.
5. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005;41 Suppl 2:S144-57.
6. Kim Y, Park GW, Kim S, et al. Fluoroquinolone and no risk of Achilles-tendinopathy in childhood pneumonia under eight years of age-a nationwide retrospective cohort. J Thorac Dis 2021;13:3399-408.
7. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. Antimicrob Agents Chemother 1997;41:1127-33.
8. Zhu C, Li Y, Yu Y, et al. Duration of antibiotic therapy in systemic lupus erythematosus patients with hospital-acquired bacterial pneumonia in eastern China. Ann Palliat Med 2021;10:2898-906.

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9. Ahn E. Introducing big data analysis using data from National Health Insurance Service. Korean J Anesthesiol 2020;73:205-11.
10. Shin DW, Cho B, Guallar E. Korean National Health Insurance Database. JAMA Intern Med 2016;176:138.
11. Kim BG, Kang D, Min KH, et al. Comparison of Cefepime with Piperacillin/Tazobactam Treatment in Patients with Hospital-Acquired Pneumonia. Antibiotics (Basel) 2023;12:984.
12. Kim BG, Kang M, Lim J, et al. Comprehensive risk assessment for hospital-acquired pneumonia: sociodemographic, clinical, and hospital environmental factors associated with the incidence of hospital-acquired pneumonia. BMC Pulm Med 2022;22:21.
13. Kumar A, Safdar N, Kethireddy S, et al. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Crit Care Med 2010;38:1651-64.
14. Arthur LE, Kizor RS, Selim AG, et al. Antibiotics for ventilator-associated pneumonia. Cochrane Database Syst Rev 2016;10:CD004267.
15. Onorato L, Macera M, Calò F, et al. Beta-lactam monotherapy or combination therapy for bloodstream infections or pneumonia due to Pseudomonas aeruginosa: a meta-analysis. Int J Antimicrob Agents 2022;59:106512.
16. Bliziotis IA, Samonis G, Vardakas KZ, et al. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. Clin Infect Dis 2005;41:149-58.
17. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 2011;11:181-9.
18. Kim MK, Han K, Lee SH. Current Trends of Big Data Research Using the Korean National Health Information Database. Diabetes Metab J 2022;46:552-63.
19. Álvarez-Marín R, López-Cerero L, Guerrero-Sánchez F, et al. Do specific antimicrobial stewardship interventions have an impact on carbapenem resistance in Gram-negative bacilli? A multicentre quasi-experimental ecological study: time-trend analysis and characterization of carbapenemases. J Antimicrob Chemother 2021;76:1928-36.

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